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TITLE: Treatment-Induced Autophagy Associated with Tumor Dormancy and Relapse

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Fort Detrick, Maryland 21702-5012

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14. ABSTRACT Studies were performed to identify the nature of chemotherapy (and radiation) induced autophagy in the MMC breast tumor cell line and the 4T1 breast tumor cell line, both of which are syngeneic and can be grown in immune competent mice. We found that the autophagy induced in the 4T1 cells was nonprotective in that its inhibition by pharmacological or genetic approaches failed to alter sensitivity to chemotherapy or radiation. In contrast, autophagy in the MMC cells was clearly cytoprotective. These differences may be related to the p53 status of the tumor cells, as the 4T1 cells are p53 null while the MMC cells are wild-type in p53. It is generally perceived that interference with autophagy will enhance sensitivity to chemotherapy and radiation; however, this premise applies solely when the autophagy is protective. Sine mutations in p53 are common in breast cancer as well as other malignancies, having a p53 null cell line may be more relevant to clinical breast cancer than a p53 wt line. Furthermore, implanting these two different cell lines in animal models will provide an opportunity to evaluate the influence of blocking autophagy (using the cells where autophagy has been genetically silenced) to recognize and eliminate the tumors. This relates to studies that tend to contradict the paradigm stating that autophagy inhibition will be therapeutically advantageous by arguing that the immune system requires an autophagic signal to recognize and eliminate the tumors. Given that autophagy and senescence have been shown to be frequently linked responses, we also demonstrated the promotion of senescence by both doxorubicin and radiation in the tumor cell lines. We recently developed an experimental technique for sorting and separating senescent and non-senescent growth arrested cells and determined that proliferative recovery occurs from both populations (using lung cancer cells). This technique will now be applied to the breast tumor cells to support the concept of tumor dormancy and recurrence associated with senescence. The senescent cells will further be grown in mice to determine their capacity to grow out post senescence as well as sensitivity to chemotherapy and radiation as models of breast cancer dormancy and disease recurrence.					
15. SUBJECT TERMS Autophagy; tumor dormancy; tumor relapse; chemotherapy; immunotherapy; senescence					
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1. **INTRODUCTION:** The objective of this project is to understand the role of autophagy in chemotherapy induced breast tumor dormancy and disease recurrence.
2. **KEYWORDS:** tumor dormancy; disease relapse, chemotherapy, autophagy senescence
3. **ACCOMPLISHMENTS:**

What were the major goals of the project?

The major goals were to understand the role of autophagy in chemotherapy induced tumor dormancy and to further understand the role of tumor interferon gamma in determining disease recurrence under immune pressure.

What was accomplished under these goals? *Please see data generated below:*

Figure 1 (panels A and B) shows the time dependent response of mouse mammary tumor cells (MMCs) to both chemotherapy (doxorubicin, Adriamycin) and irradiation (one dose of 6 Gy). In both cases, the impact is prolonged growth arrest rather than cell death. In the case of doxorubicin, growth arrest is succeeded by proliferative recovery while in the case of radiation, the growth arrest is prolonged, with no immediate evidence for recovery. However, these studies are currently being repeated for an extended period of time and are also demonstrating recovery from radiation-induced senescence.

Initial studies to evaluate autophagy were based on acridine orange staining, which is shown in **Figure 1C (upper panels)**. The cells also demonstrated senescence, based on beta galactosidase staining (**Figure 1C, lower panels**). The induction of autophagy was confirmed by the formation of LC3B (**Figure 1D**) and degradation of p62/SQSTM1 (**Figure 1E**) while the promotion of senescence was confirmed by the induction of p21 (**Figure 1F**) and secretion of HMGB1 (**Figure 1G**). **Figure 1H** indicates that the MMC cells are wild type in p53, which will be shown to have direct relevance to the nature of autophagy in the data presented below.

In previous work, we have reported that autophagy can be either cytoprotective or nonprotective . To determine the function of autophagy, cells were treated with the pharmacological autophagy inhibitor, chloroquine or silenced for the autophagy gene, ATG5 (**Figure 2A**). **Figure 2B** confirms that autophagy was inhibited based on interference with the degradation of p62/SQSTM1 and reduced formation of LC3B. Under both conditions, drug and/or radiation sensitivity were enhanced (**Figure 3**), substantiating the cytoprotective function of autophagy in this experimental model.

Although there is evidence for a close association between autophagy and senescence, our laboratory as well as other investigators have demonstrated that the two responses are dissociable in that senescence is delayed when autophagy is inhibited but not abrogated. In the studies presented in **Figures 1F and 1H**, we demonstrate that even in the presence of the autophagy

inhibitor, chloroquine, neither induction of p53 nor p21 is suppressed, consistent with the conclusion that senescence is not dependent on autophagy. In ongoing studies, we have generated additional data indicating that senescent growth arrest is maintained even in the presence of the autophagy inhibitor, chloroquine. Furthermore, proliferative recovery post senescence is not compromised, essentially indicating that the senescence response is intact in autophagy compromised cells.

Similar studies to those described for the MMC cells were performed in the 4T1 breast tumor cells. It should be noted that 4T1 cells are null for p53 while the MMC cells clearly express p53 (**Figure 1H**). Again, as was the case with the MMC cells, growth arrest by both doxorubicin and radiation is followed by proliferative recovery (**Figures 4A and 4B**). Furthermore, both doxorubicin and radiation promoted both autophagy and senescence (**Figure 4C and Figure 5A**). However, in contrast to the MMC studies, the autophagy in 4T1 cells was nonprotective, as chloroquine failed to significantly alter the time course response or clonogenic survival (**Figures 4A and 4B, 4D and 4E**). Furthermore, as was the case with the MMC cells, inhibition of autophagy did not interfere with drug or radiation induced senescence (**Figures 5B and 5C**).

Overall, these data suggest that both autophagy and senescence are induced in breast cancer cells by conventional therapies and could contribute to tumor dormancy and ultimately to disease recurrence.

Discussion and Relevance:

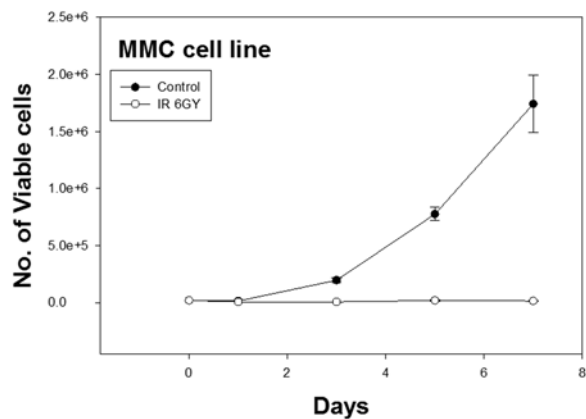
We did not find it surprising that the chemotherapeutic drug, doxorubicin, as well as ionizing radiation promote both autophagy and senescence in the breast tumor cell models being utilized for the current work as we (as well as others) have shown autophagy to be a primary first response to different forms of stress in various tumor cell lines (1,2) . Furthermore, we have observed senescence rather than programmed cell death in a variety of tumor cell models when exposed to doxorubicin or radiation (when these modalities were utilized at concentrations/doses that would be considered to be clinically relevant) (3,4,5). However, it is somewhat unexpected that senescence was evident also in the 4T1 cell line that is null in p53 since it has often been thought that functional p53 is required for the senescence response (3).

The interesting findings are as follows. Proliferative recovery is observed from autophagic/senescent cell populations. This is consistent with the hypothesis we have been promoted previously that senescence is actually reversible (6) and that senescence arrest and proliferative recovery may be components of tumor dormancy and disease recurrence (7). We plan to develop and explore this possibility further when the senescent tumor cells are implanted into animal models in collaboration with Dr. Manjili, the initiating PI on this project.

We have further been able to dissociate senescence from autophagy in these experimental systems, which supports our previous findings that while these responses tend to occur collaterally, they are nevertheless independent of each other (8).

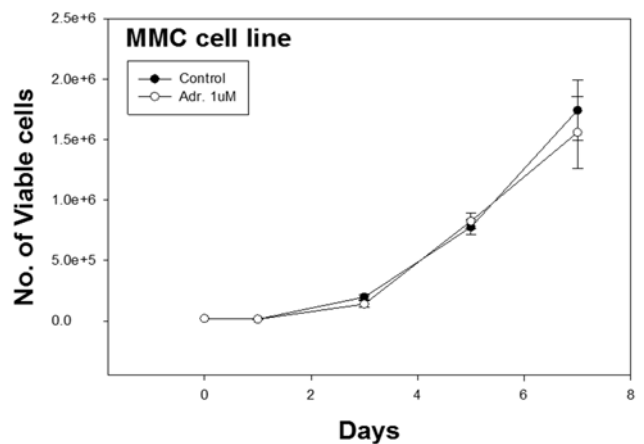
It will also be of particular interest to compare the immune response to the induction of autophagy in the MMC cell line and the 4T1 cells. There are a few studies in the literature that suggest that the immune system recognizes and eliminates cells that are autophagic due to the secretion of factors such as ATP (9); however, this is not an established paradigm and one of our primary goals is to understand how the immune system responds to autophagic cells, again in collaboration with Dr. Manjili's laboratory.

The fact that autophagy is protective in the MMC cells and nonprotective in the 4T1 cells (10) adds an additional wrinkle to the studies in that we may expect that the immune response to the tumor cells could differ when the autophagy is functionally different. However, these studies may be somewhat difficult to interpret given that the cells are non-isogenic. We will consider whether it may be productive to either silence p53 in the MMC cells or induce p53 in the 4T1 cells.



A

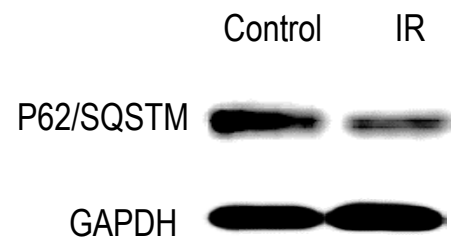
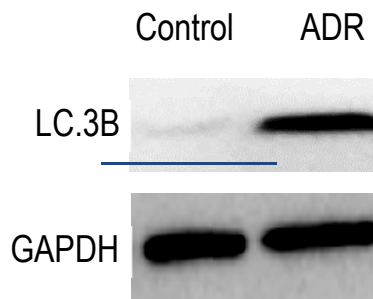
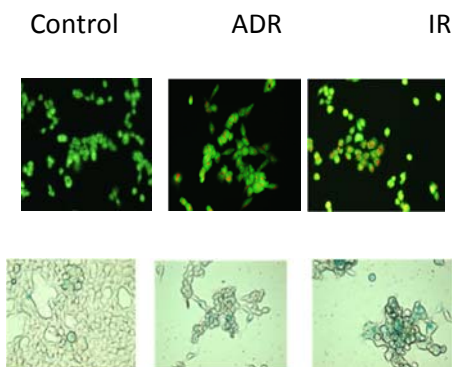
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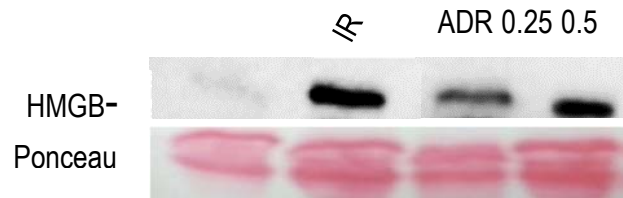
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F.



G.



H.

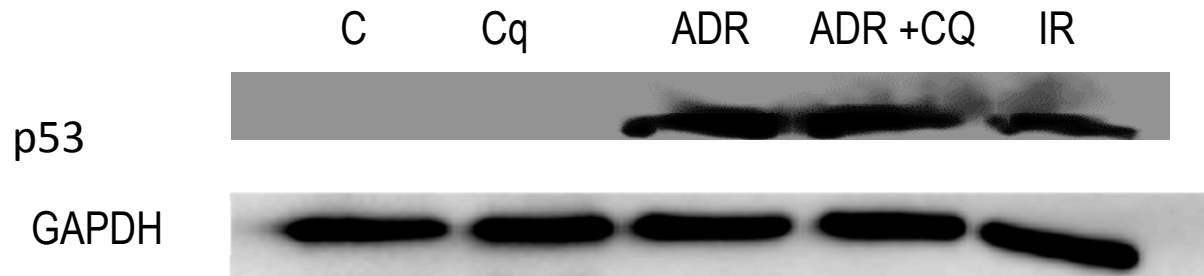
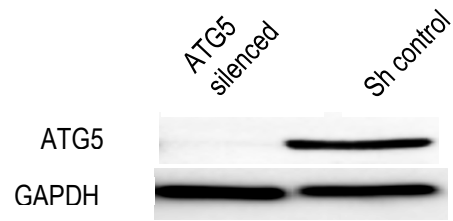


Figure 1. Autophagy and senescence induction in MMC breast tumor cells in response to Adriamycin (ADR) or Ionizing radiation (IR): MMC cells were treated with ADR (1uM) for 2h for three days or IR (6 Gy). Panels A and B show the temporal response to treatment. Cells were stained with acridine orange (AO) for detection of autophagosomes (Panel C, upper portion) and beta galactosidase (β -gal) as a marker of senescence (panel C, lower portion). Induction of autophagy was confirmed by Western blotting for appearance of LC3B and degradation of p62 (Panels D and E). Induction of p21 (Panel F) and p53 (Panel H) were not suppressed by chloroquine, suggesting that autophagy and senescence are dissociable. Secretion of HMGB1 into the incubation medium (Panel G) is indicative of the promotion of autophagy and/or senescence by doxorubicin (Adriamycin, ADR)

A.



B.

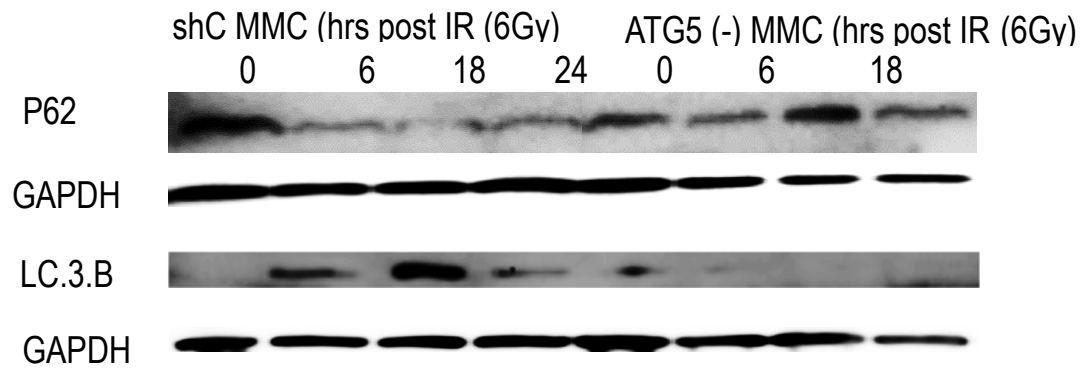


Figure 2. Silencing of autophagy in MMC cells. **(A)** Sh RNA mediated silencing of the autophagy gene, ATG5, in MMC cells. **(B)** Interference with degradation of p62 indicative of silencing of autophagy. Reduced formation of LC3 B confirming the silencing of autophagy.

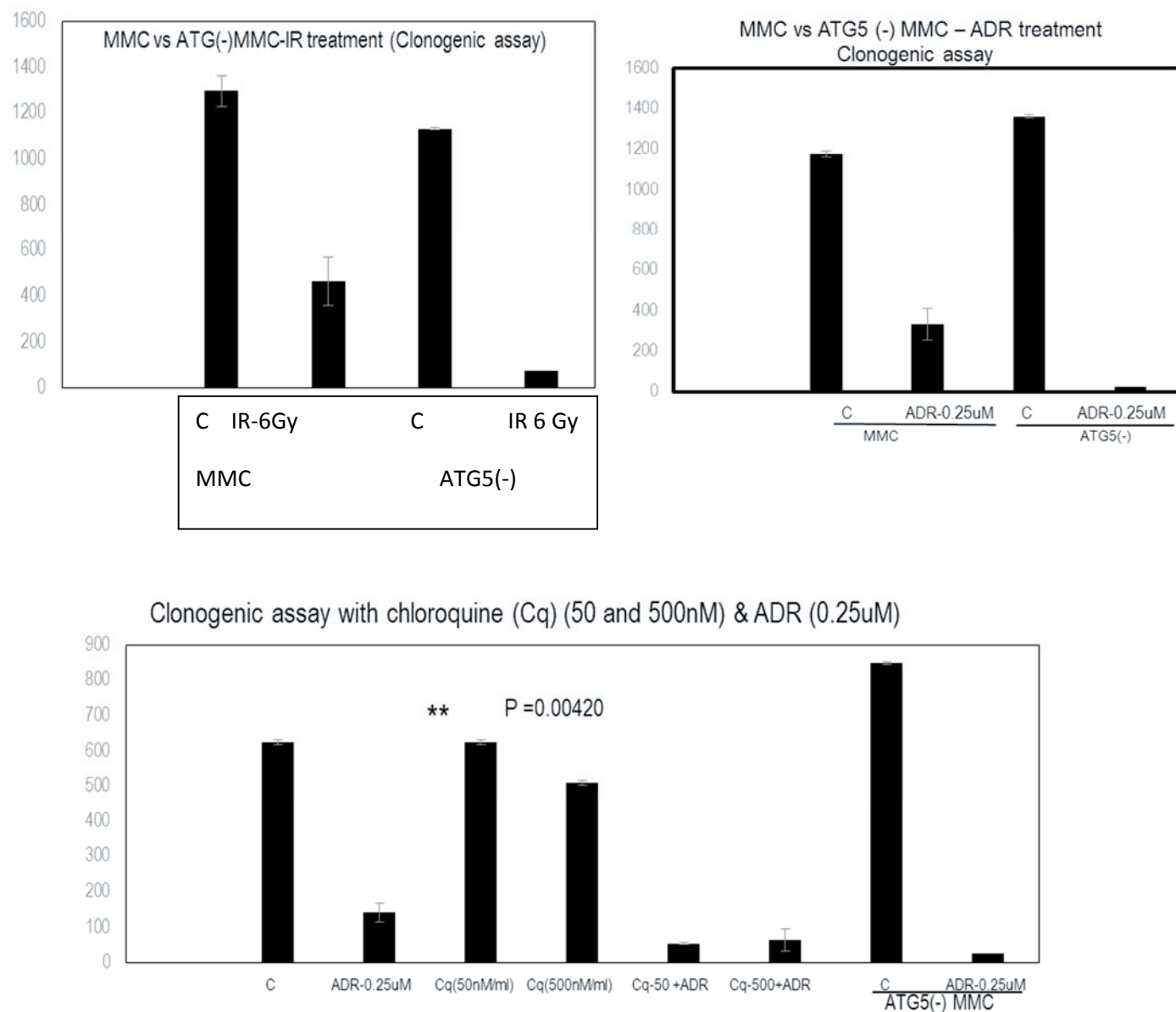


Figure 3. Adriamycin and ionizing radiation promote cytoprotective autophagy in MMCs: ATG5 (-) and shControl MMCs were treated with IR (6Gy), ADR (0.25uM) and/or CQ (50 and 500nM) and clonogenic survival assessed. Upper Left Panel: Enhanced sensitivity to radiation (IR) with genetic silencing of autophagy (Upper right figure) Enhanced sensitivity to ADR with genetic silencing of autophagy (C) Enhanced sensitivity to ADR with pharmacologic or genetic inhibition of autophagy.

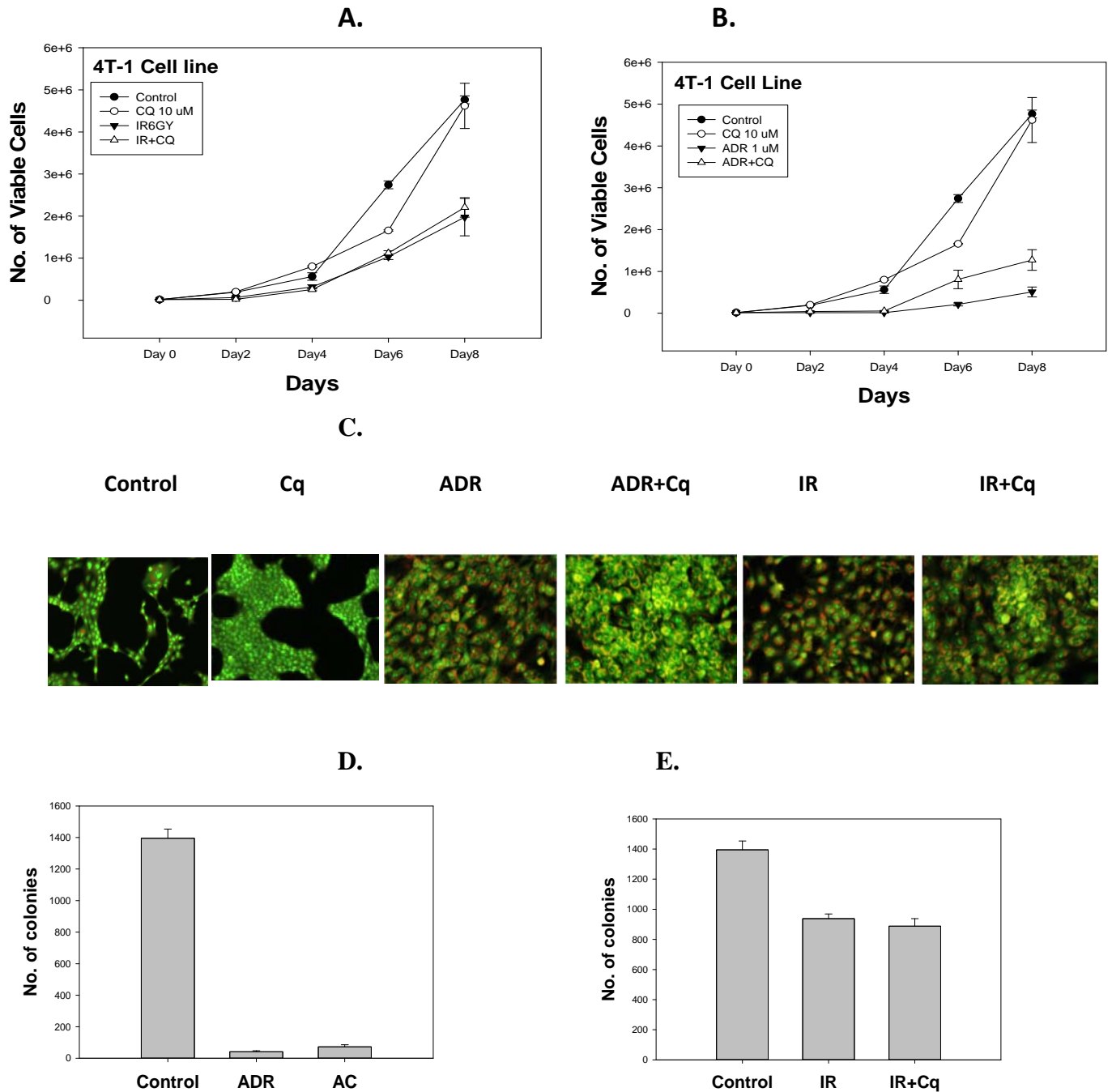


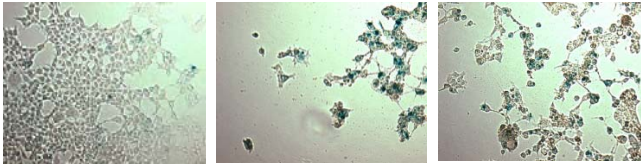
Figure 4. Senescence and proliferative recovery in response to Chemotherapy and Ionizing Radiation in 4T1 mammary tumor cells. 4T1 cells were treated with ADR (1uM) for 2h or IR (6 Gy). Panels A and B show transient arrest followed by proliferative recovery and lack of sensitization by chloroquine. Panel C: Evidence for promotion of autophagy by Adriamycin and radiation and inhibition of autophagy (change of staining from orange to yellow based on interference with acidification). Panels D and E: Lack of sensitization by chloroquine in clonogenic survival assays.

A.

Control

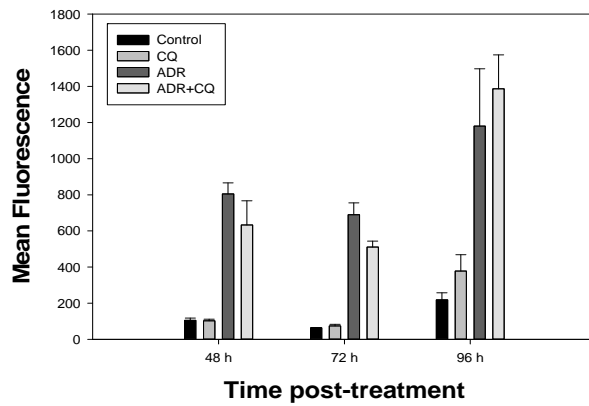
ADR

IR



B.

Time course ADR



C.

Time course IR

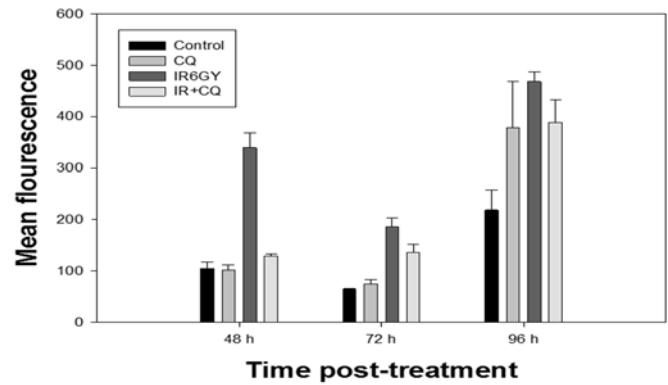


Figure 5. Senescence induced in 4T1 cells by Adriamycin and Radiation. Panel A shows beta galactosidase staining of 4T1 mammary tumor cells after drug or radiation exposure. Panels B and C indicate that chloroquine fails to interfere with the extent of senescence induced by either Adriamycin or senescence, strongly suggesting that the two responses are dissociable.

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What opportunities for training and professional development has the project provided?

The project provided for the training and professional development of Dr. Theresa Thekkudan and Ms. Liliya Tyutyunyik-Massey, a PhD candidate in Dr. Gewirtz's laboratory.

How were the results disseminated to communities of interest?

The results have been disseminated in poster presentations at local (Massey Cancer Center, Virginia Commonwealth University) and national (American Association for Cancer Research) scientific meetings and in published papers.

What do you plan to do during the next reporting period to accomplish the goals?

One of our primary goals will be to work with the Initiating Investigator, Dr. Manjili, to establish the nature of the immune response to the different forms of autophagy in tumor bearing animals.

An additional and primary goal will be to sort senescent arrested from non-senescence arrested breast tumor cells in culture and demonstrate proliferative recovery as a potential in vitro model of tumor dormancy and recovery. These cells that are both autophagic and senescent will then be injected into immune competent animals to determine their capacity to emerge from a state of senescence (i.e. tumor dormancy) and regrow and their sensitivity (or lack thereof) to chemotherapy and radiation.

The following experiments are also planned to further develop the preliminary findings presented above:

1. Use of the pharmacological inhibitors of autophagy, bafilomycin and 3-methyl adenine to confirm the nature of autophagy in the breast tumor cell lines.
2. Genetic silencing of autophagy in the 4T1 breast tumor cell line.
3. Assessment of apoptosis induction for both doxorubicin and radiation.
4. Quantification of autophagy by Flow cytometry (time course)
5. Quantification of senescence by Flow cytometry (time course)
6. Assessment of autophagic flux based on degradation of p62/SQSTM1
7. Confirmation that senescence induced by doxorubicin (or irradiation) is not eliminated when autophagy is blocked pharmacologically
8. Confirmation that senescence induced by doxorubicin (or irradiation) is not eliminated when autophagy is blocked genetically
9. Sorting of cells and replating of senescent and non-senescent cells to demonstrate recovery of proliferative capacity in both populations.
10. Tumor bearing animal studies to determine whether autophagic/senescent cells are in a state of dormancy from which the cells can recover...and the impact of immune surveillance on recovery.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Salient findings:

Autophagy and senescence are primary response to chemotherapy and radiation in the breast tumor cells.

Proliferative recovery is observed from autophagic/senescent cell populations.

Autophagy and senescence are dissociable.

Autophagy is protective in the p53 wt MMC cells and nonprotective in the p53 null 4T1 mammary tumor cells.

What was the impact on other disciplines?

None to report

What was the impact on technology transfer?

None to report

What was the impact on society beyond science and technology?

None to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

We have not changed the experimental approaches proposed in our grant and statement of work. However, we have incorporated studies involving radiation (generally as a positive control for the induction of autophagy), included experiments relating to the promotion of senescence (as autophagy and senescence have been shown to be closely linked responses by a number of laboratories, including our own) and have added studies using the well-established 4T1 breast tumor cell line. As will be evident from the experimental data presented above, the advantage of also performing complementary studies in the 4T1 cell line is the possibility of studying the influence of both cytoprotective autophagy using the MMC cells and nonprotective autophagy using the 4T1 cells. In this context, nonprotective autophagy in response to both chemotherapy and radiation is phenomenon that our laboratory has discovered and established in the literature.

Actual or anticipated problems or delays and actions or plans to resolve them:

The postdoctoral fellow who was originally working on this project, Theresa Thekkudan, unexpectedly became pregnant and had a very difficult delivery that involved a number of residual medical problems. She has been unable to work since the beginning of this year (2015) and will not be returning to the laboratory. Fortunately, she had trained a Ph.D. candidate in my laboratory, Liliya Tyutyunyk-Massey, who will now have this research as the focus of her PhD degree. Nevertheless, since Liliya is a student in training, it is taking some time for her to develop the appropriate laboratory skills necessary to carry out the proposed experimental studies. Consequently, the output of experimental data for this project will be delayed for a period of approximately 6-9 months.

Changes that had a significant impact on expenditures

Given that Dr. Thekkudan was obligated to take medical leave, her salary was not charged to the grant for a period of approximately 6 months. Beginning July 1st, stipend and tuition support for Ms. Tyutyunyk-Massey will be charged to the grant. We further anticipate that the changeover in personnel will require us to request a no-cost extension to allow this PhD student to carry out the experimental approaches that were proposed in the grant.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

None

6. PRODUCTS:

- Publications, conference papers, and presentations

Alotaibi M, Sharma K, Saleh T, Povirk LF, Hendrickson EA and Gewirtz D.A. Radiosensitization by PARP Inhibition in DNA Repair Proficient and Deficient Tumor Cells: Proliferative Recovery in Senescent Cells. *Radiation Research*, 2016 Mar;185(3):229-45. *This paper established the novel methodology that will be utilized to separate senescent and non-senescent breast tumor cells for studies both in cell culture and in tumor bearing animals.*

Gewirtz, D, Alotaibi M, Yakovlev V, Povirk LF. Tumor cell recovery from senescence induced by radiation + PARP inhibition. *Radiation Research*. In press. *This paper addresses that possibility that senescence represents an undesirable response to therapy in potentially allowing for the survival of tumor cells in state of dormancy from which the cells may ultimately emerge to promote disease recurrence.*

Chakradeo S, Elmore LW, Gewirtz DA. Is Senescence Reversible? *Curr Drug Targets*. 2016;17(4):460-6. *This review presents the unorthodox viewpoint that senescence induced by chemotherapy and radiation in tumor cells is ultimately reversible, contributing to disease recurrence.*

Chakradeo S, Sharma K, Alhaddad A, Bakhshwin D, Le N, Harada H, Nakajima W, Yeudall WA, Torti SV, Torti FM, Gewirtz DA. Yet another function of p53: the switch that determines whether radiation-induced autophagy will be cytoprotective or nonprotective. Implications for autophagy inhibition as a therapeutic strategy. *Mol Pharm* 2015;87(5):803-14. *This work further develops the theme of nonprotective autophagy, which is directly relevant to the studies using the 4T1 breast tumor cell line.*

American Association for Cancer Research 2016 Meeting
Theresa Thekkudan, Supriya Joshi (Manjili laboratory), David Gewirtz. Induction of cytoprotective autophagy and senescence in response to chemotherapy and ionizing-radiation as possible mechanisms of tumor dormancy

Proliferative recovery in tumor cells subsequent to chemotherapy and/or radiation-induced prolonged growth arrest may prove to represent a state of autophagy and/or senescence. This may also be useful as an in vitro model of tumor dormancy. To explore this hypothesis, studies were performed in primary mouse mammary carcinoma cells (MMC) treated with Adriamycin (ADR) (0.25uM - 1uM) for 3 days (2h each) and ionizing radiation (IR) (6Gy). Promotion of autophagy was confirmed based on detection of autophagosomes based on acridine orange staining, the appearance of the autophagy marker, LC3.B, associated with autophagosome, degradation of p62/SQSTM1, a hallmark of autophagic flux (i.e. the completion of autophagy and degradation of autophagosome content). Autophagosome formation was observed 24h post ADR treatment and 72h post IR treatment. Furthermore, to understand the function of autophagy

(cytoprotective, nonprotective or cytotoxic) autophagy was blocked either pharmacologically using chloroquine (CQ) or genetically by silencing of the key autophagy gene, ATG5. LC3.B appearance and p62/SQSTM1 degradation were more pronounced in wt (autophagy proficient) cells compared to ATG5 silenced cells, confirming that autophagy was inhibited by these pharmacological and genetic strategies. Furthermore, interference with autophagy sensitized the MMC cells to ADR and radiation. These observations indicated that ADR and IR induced autophagy was cytoprotective in the MMC cells. Unexpectedly, apoptosis (as measured by PI/Annexin V assay) was not increased in response to either ADR alone or the combination of ADR and CQ, suggesting that sensitization was likely occurring through alternative pathways. An evaluation of select markers of senescence indicated enhanced expression of p21 as well as enhanced secretion of the autophagy/senescence associated marker, HMGB1, in response to Adriamycin and IR. Overall, these data suggest that both autophagy and senescence are induced in breast cancer cells by conventional therapies and could contribute to tumor dormancy. Inhibition of autophagy and/or senescence associated signaling pathways could lead to therapeutic strategies for interfering with proliferative recovery of tumor cells after standard modes of therapy. Studies are currently in progress to determine whether the senescence associated secretory phenotype (SASP) accompanies the induction of senescence. SASP has been associated with promotion of tumor growth and alternatively, with activation of an immune response to therapy.

Papers

Presentations

- **Website(s) or other Internet site(s)**

- **Technologies or techniques**

- **Inventions, patent applications, and/or licenses**

- **Other Products**

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Dr. David Gewirtz

Dr. Theresa Thekkudan

Ms. Liliya Tyutyunyk-Massey

Mr. Tareq Saleh (other source of support)

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes. The PI was awarded an NIH grant on the topic of mitigation of peripheral neuropathy induced by cancer chemotherapeutic drugs in collaboration with Dr. Imad Damaj in the Department of Pharmacology and Toxicology.

What other organizations were involved as partners?

None

8. SPECIAL REPORTING REQUIREMENTS:

COLLABORATIVE AWARDS:

9. APPENDICES: